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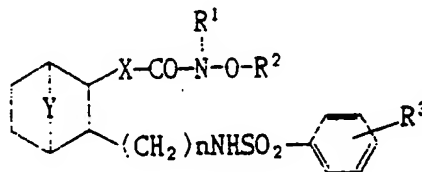
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(54) Sulfonlamino substituted bicycyl hydroxamic acid derivatives.

(57) Sulfonlamino substituted bicycyl hydroxamic acid derivatives of the formula:



wherein R<sup>1</sup> and R<sup>2</sup> each is hydrogen or lower alkyl; R<sup>3</sup> is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2 or the pharmaceutically acceptable salt thereof. These compounds have an advanced antagonistic activity to thromboxane A<sub>2</sub> (TXA<sub>2</sub>)-receptor and are useful for the treatment of thrombosis, vasoconstriction, or bronchoconstriction, and the like disease which are induced by TXA<sub>2</sub>.

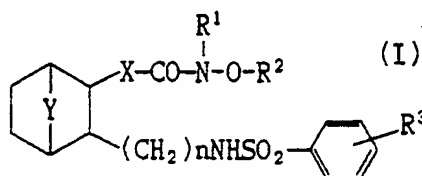
EP 0 453 960 A1

The present invention relates to compounds with an advanced antagonistic activity to thromboxane A<sub>2</sub> - (TXA<sub>2</sub>)-receptor, in more detail, to sulfonylamino substituted bicyclic hydroxamic acid derivatives or the pharmaceutically acceptable salts thereof, which are suitable for use in the treatment of thrombosis, vasoconstriction, or bronchoconstriction, and the like disease which are induced by TXA<sub>2</sub>.

It has been reported that sulfonylamino substituted bicyclic carboxylic acid derivatives (hereinafter referred to carboxylic acid derivatives) have potent TXA<sub>2</sub>-receptor antagonistic activities (JP-A-63-139161, US-A-4,654,357, EP-A-312,906, and DE-A-37 20 760).

These carboxylic acid derivatives have some drawback that they are easily oxidized and metabolized in living tissues. Therefore it has been desired to develop TXA<sub>2</sub>-receptor antagonists, which are pharmacologically comparable to, but are biologically stabler than the carboxylic acid derivatives.

The present invention relates to hydroxamic acid derivatives of the following formula (I):



wherein  $R^1$  and  $R^2$  each is hydrogen or lower alkyl;  $R^3$  is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2. They are very useful for use in the prevention and the treatment of thrombosis, vasoconstriction, or bronchoconstriction, and the like disease because of their high inhibitory activity against platelet aggregation.

In the present specification, "lower alkyl" means C<sub>1</sub>-C<sub>6</sub> alkyl, including, for example, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, and hexyl. Preferred is methyl, ethyl, or propyl.

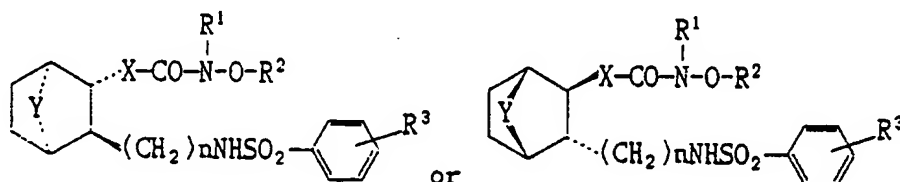
"Lower alkoxy" means C<sub>1</sub>-C<sub>6</sub> alkyloxy, including, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, and hexyloxy. Preferred is methoxy, ethoxy, or propoxy.

"Halogen" means fluorine, chlorine, bromine, or iodine.

"Alkylene" means C<sub>4</sub>-C<sub>7</sub> alkylene, including, for example, tetramethylene, pentamethylene, hexamethylene, and heptamethylene.

"Alkenylene" means C<sub>4</sub>-C<sub>7</sub> alkenylene, including, for example, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, 5-hexenylene, 1-heptenylene, 2-heptenylene, 3-heptenylene, 4-heptenylene, 5-heptenylene, and 6-heptenylene. Preferred is 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, or 5-hexenylene.

The compounds of the present invention are hydroxamic acid derivatives as explicated by the formula, so such a pharmaceutically acceptable salt as anticipated by a person with ordinary skill in this art is included in the scope of the present invention. Furthermore, the compounds of the present invention have four asymmetric centers as shown in the formula (I) and therefore the scope of this invention extends to all the possible stereoisomers. Among others, it is most preferable to use the present compounds in an optically active form of the following formula:



wherein  $R^1$ ,  $R^2$ ,  $R^3$ , X, Y, and n each is the same as defined before, but is enough to use them with an optical impurity for the purpose of this invention because of their remarkably high activities.

Furthermore, in the case  $R^1$  is hydrogen in the formula (I), the tautomers thereof are also included in the scope of the present invention.

It is thought that the hydroxamic acids moieties at the 2-position of the bicyclic skeleton contribute to an improvement on the effects to the biological stability and/or the partial agonistic action.

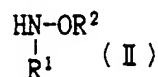
Therefore, lower alkyl, lower alkoxy, hydroxy, or halogen as a substitution on phenyl or phenylsulfonylamino group which is another side chain may be substituted at any position.

5 Preferred are those compounds which are unsubstituted or substituted by methyl, hydroxy, chloro, or bromo at the 4-position of the phenyl in the light of their main effect. Hydroxy may be esterified with acetyl etc.

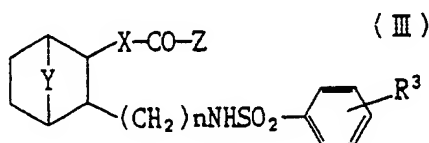
Furthermore, it can be expected that conversion of carboxylic acids to hydroxamic acid derivatives improves the biological stability and/or decreases partial agonistic action in thromboxane A<sub>2</sub>-receptor antagonists.

10 The acceptable salts of the compounds of the present invention mean salts formed with an alkali metal such as lithium, sodium, or potassium, an alkaline earth metal such as calcium or magnesium; an organic base such as triethylamine, azetidine, 2-phenylimidazole, 1,4-diaminobutane, n-butylcyclohexylamine, dicyclohexylamine, hexamethylenediamine, 3-methyl-3-aminopentane, piperidine, 2,2,6,6-tetramethyl-  
15 piperidine, 2,2,4-trimethylpiperidine, 2-hydroxypyridine, 4-hydroxypyridine, 2,4,6-trimethylpyridine, tetrahydro-2-methylpyridine, or pyrrolidine. Particularly the salt formed with sodium, potassium, or calcium etc. is preferable.

The compounds (I) of the present invention can be prepared, for example, by condensing amines of the formula (II):



25 wherein R<sub>1</sub> and R<sub>2</sub> each is the same as defined before, with the compounds of the formula (III):



30 wherein R<sup>3</sup>, X, Y, and n each is the same as defined before; and Z means an electron withdrawing group.

"Electron withdrawing group" means any of groups which can activate carbonyl. Those used in a usual acylating reaction may be employed.

The present reaction may be performed according to a conventional manner for synthesizing hydroxamic acids, which is disclosed in ORGANIC CHEMISTRY, Vol.12 III, 406-432 (Academic Press).

40 The starting materials may be prepared according to the disclosure in JP-A-63-139161, JP Patent Application 1-314028, US-A-4, 654,357, or EP-A-312,906.

The compounds of the present invention can inhibit effects caused by thromboxane A<sub>2</sub>, so are very useful for use in the prevention and the treatment of inflammation, hypertension, thrombosis, cerebral apoplexy, cardiac infarction, and cerebral infarction.

45 Furthermore, known TXA<sub>2</sub>-receptor antagonists give very preferable biological effects if in such an oral administration as to give a mild elevation of the blood level of the drug, but unfavorable in the light of side effects if in such an one-shot intravenous injection as to rapidly give a high blood level, because of their TXA<sub>2</sub>-receptor agonistic action (partial agonistic action) after administration, although they are transient.

50 On the other hand, the compounds of the present invention has substantially no or reduced partial agonistic activities, as explained in the later parts. As stated before, it is needless to say that those which have no or substantially no partial agonistic activities are particularly suitable for injection use. Furthermore, if necessary, the compounds of the present invention can be formulations for inhalation, oral, or suppository use, because of their good stability and absorbability.

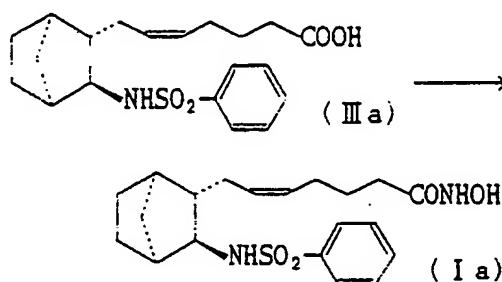
55 The compounds of the present invention may be used in conventional formulations for oral use, including solid preparations such as tablets, powder, capsules, and granules, and liquid preparations such as aqueous or oily suspensions, syrups, and elixirs. For the parenteral use, the compounds of the present invention may be aqueous or oily suspensions for injection. When preparing such the formulations,

conventional additives may be used, such as fillers, binders, lubricants, aqueous or oily solvents, emulsifiers, and suspending agents, and additionally, preservatives, stabilizers, or the like. It is hard to generally define the dosage of the compounds (I) of the present invention because it depends on the objective therapeutic effects, administration routes, ages, body weights etc. But usual daily dosage per kg of body weight for an adult is about 0.01 mg to about 50 mg, preferably about 0.05 mg to about 10 mg orally, and about 0.001 mg to about 5 mg, preferably about 0.005 mg to about 1 mg parenterally; in one to five divided doses.

The present invention is further embodied in the following Examples and Experiments, which are not intended to limit the scope of the present invention.

#### Example 1

Preparation of (1R,2S,3S,4S)-(5Z)-7-(3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)-5-heptenohydroxamic acid (Ia)



To a solution of (1R,2S,3S,4S)-(5Z)-7-(3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)-5-heptenoic acid (IIIa) (1.133g, 3mM) in dichloromethane (10ml) is added oxalylchloride (915 $\mu$ l, 3mM $\times$ 3.5) under nitrogen atmosphere at room temperature and the mixture is refluxed under mild (50 $^{\circ}$ C) conditions. After 1 hour, the reaction mixture is evaporated to leave a residue, then benzene is added thereto and the mixture is evaporated again to remove the excess of reagent. Hydroxylamine hydrochloride (1.04g, 3mM $\times$ 5) is suspended in THF (10ml), then a saturated aqueous solution of NaHCO<sub>3</sub> (10ml) is added thereto at room temperature and the mixture is stirred for 5 minutes. To the reaction mixture is added a solution of the acid chloride, prepared before, in THF (6ml) at room temperature and the mixture is stirred vigorously 1.5 hours. The resulting solution is partitioned between ethyl acetate and 0.5N hydrochloric acid. Then the organic solution is washed with water, dried, and evaporated under reduced pressure to leave a residue, which is recrystallised from dichloromethane/ether to give the objective compound (Ia) (910mg, yield: 77.1%).

colorless pillars mp. 98-100 $^{\circ}$ C

IR(Nujol)  $\nu$  max: 3340, 3246, 1648, 1161, 1093, 1059, 758, 717, 687 cm<sup>-1</sup>.

<sup>1</sup>HNMR(CDCl<sub>3</sub>)  $\delta$  ppm: 0.95-2.30(m, 17H), 3.00-3.13(m, 1H), 5.20-5.43(m, 2H), 5.75(d, J = 7Hz, 1H), 7.45-7.65(m, 3H), 7.80-7.95(m, 2H).

[ $\alpha$ ]<sub>D</sub> +23.7 $\pm$ 0.6 $^{\circ}$  (CH<sub>3</sub>OH, 1.011%, 25.5 $^{\circ}$ C).

Elementary Analysis Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S (%):

C 61.19, H 7.20, N 7.14, S 8.17,

Found. (%): C 61.20, H 7.17, N 7.15, S 8.25.

#### Sodium salt of the compound (Ia)

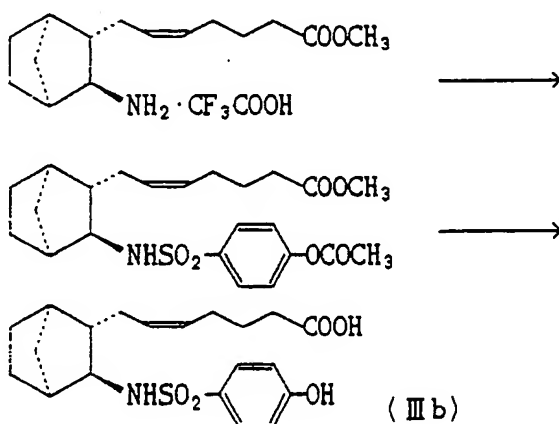
To a solution of the compound (Ia) (196mg, 0.5mM) in methanol (3ml) is added sodium methoxide (0.163N/methanol) (3.06ml, 0.5mM) at 0 $^{\circ}$ C, and the mixture is stirred for a few minutes, then evaporated

under reduced pressure to leave a residue, which is dissolved in water, and lyophilized to give quantitatively the sodium salt of the compound (Ia) (207mg) as a colorless powder.

## Example 2

Preparation of (1R,2S,3S,4S)-(5Z)-7-[3-(4-hydroxyphenylsulfonylamino)bicyclo[2.2.1]hept-2-yl]-5-heptenohydroxamic acid (Ib)

(1)



To a solution of methyl (1R,2S,3S,4S)-(5Z)-7-[3-aminobicyclo[2.2.1]hept-2-yl]-5-heptenoate trifluoroacetic acid salt (548mg, 1.5mM) in dichloromethane (4ml) is added a solution of triethylamine (625μl, 1.5mM×3) and p-acetoxyphenylsulfonylchloride (360mg, 1.5mM) in dichloromethane (2ml) under nitrogen atmosphere at 0°C, and the mixture is stirred for 20 minutes at the same temperature. The resulting solution is partitioned between ethyl acetate and 2N hydrochloric acid, then the organic solution is washed with water, dried, and evaporated under reduced pressure to leave a residue. Chromatography on silicagel with toluene-ethyl acetate (9:1) as the eluent gave the corresponding sulfonamide (310mg, yield:45.9%) as a colorless gum.

To a solution of the compound (300mg, 0.66mM) in methanol (3ml) is added a solution of 1N KOH (2.64ml, 0.66mM×4) at room temperature, and the mixture is stirred for 4 hours. The resulting solution is partitioned between toluene and water, then the aqueous solution is acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extract is washed with water, dried, and evaporated under reduced pressure to give 258mg of the hydroxy compound of the sulfonamide (IIIb) quantitatively as a colorless gum.

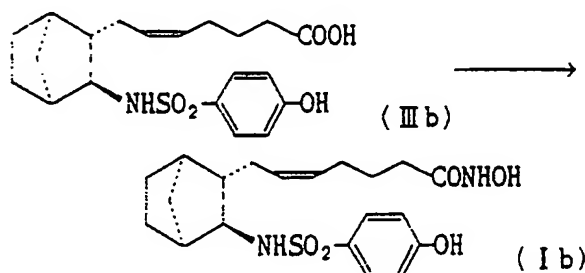
<sup>1</sup>HNMR(CD<sub>3</sub>OD) δ ppm: 0.96-2.05(m, 14H), 2.12-(brs, 1H), 2.25(t, J=7.4Hz, 2H), 2.85-2.93(m, 1H), 5.10-5.33 (m, 2H), 6.85-6.95(m, 2H), 7.65-7.75(m, 2H)

(2)

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The compound (Ib) of the present invention and its sodium salt are prepared according to the same manner as in Example 1.

Yield: 26.4%, colorless foam.  
 IR(Nujol)  $\nu$  max: 3270, 1642, 1604, 1587, 1500, 1148, 1093, 837, 677  $\text{cm}^{-1}$ .  
 $^1\text{H NMR}(\text{CD}_3\text{OD})$   $\delta$  ppm: 0.97-2.15(m, 17H), 2.85-2.95(m, 1H), 5.10-5.35(m, 2H), 6.85-6.95(m, 2H), 7.65-7.75(m, 2H)  
 $[\alpha]_D^{25} +17.5 \pm 1.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  0.561,  $22.0^\circ\text{C}$ )

Elementary Analysis Calcd. for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_5\text{S} \cdot 0.2\text{H}_2\text{O}$  (%):

C 58.28, H 6.96, N 6.80, S 7.78,

Found. (%): C 58.47, H 7.02, N 6.81, S 7.35.

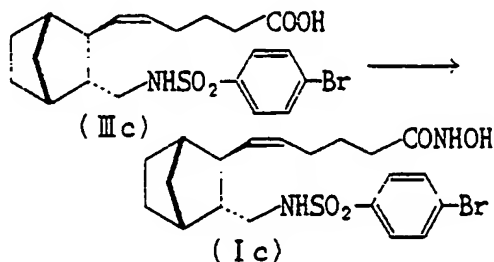
### 35 Example 3

Preparation of (1S,2S,3R,4R)-(5Z)-6-[3-(4-bromophenylsulfonylaminomethyl)bicyclo[2.2.1]hept-2-yl]-5-hex-enohydroxamic acid (Ic)

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The compound (Ic) of the present invention and its sodium salt are prepared according to the same manner as in Example 1.

Yield: 42.5%, colorless foam.  
 IR( $\text{CHCl}_3$ )  $\nu$  max: 3360, 1662, 1577, 1471, 1405, 1391, 1331, 1160, 1093, 1069 1009, 820, 601  $\text{cm}^{-1}$ .

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  ppm: 1.10-2.35(m, 16H), 2.75-3.10(m, 2H), 4.95-5.30(m, 2H), 5.27(d,  $J=9\text{Hz}$ , 1H),  
7.62-7.83(m, 4H).  
 $[\alpha]_D + 15.3 \pm 0.5^\circ$  ( $\text{CH}_3\text{OH}$ , c 1.018%,  $25.5^\circ\text{C}$ )

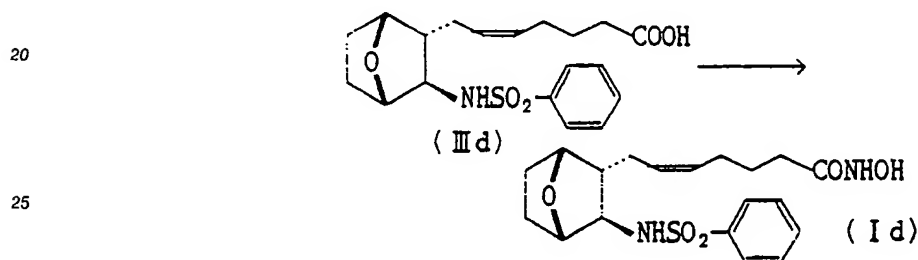
Elementary Analysis Calcd. for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_4\text{SBr} \cdot 0.4\text{H}_2\text{O}$  (%):

C 50.18, H 5.87, N 5.85, S 6.70

Found. (%): C 50.24, H 5.85, N 6.01, S 6.78.

#### Example 4

Preparation of (1R\*,2R\*,3R\*,4S\*)-(5Z)-7-[3-phenylsulfonylamino-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenohydroxamic acid (Id)



The compound (Id) of the present invention and its sodium salt are prepared according to the same manner as in Example 1.

Yield: 67.4%, colorless foam.

IR( $\text{CHCl}_3$ )  $\nu$  max: 3350, 1664, 1447, 1343, 1327, 1160, 1093, 982, 583  $\text{cm}^{-1}$ .

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  ppm: 1.20-2.30(m, 13H), 2.86-3.00(m, 1H), 4.02(d,  $J=4.3\text{Hz}$ , 1H), 4.42(brs, 1H),  
5.10-5.37(m, 2H), 5.63(d,  $J=9.0\text{Hz}$ , 1H), 7.47-7.66(m, 3H), 7.84-8.00(m, 2H).

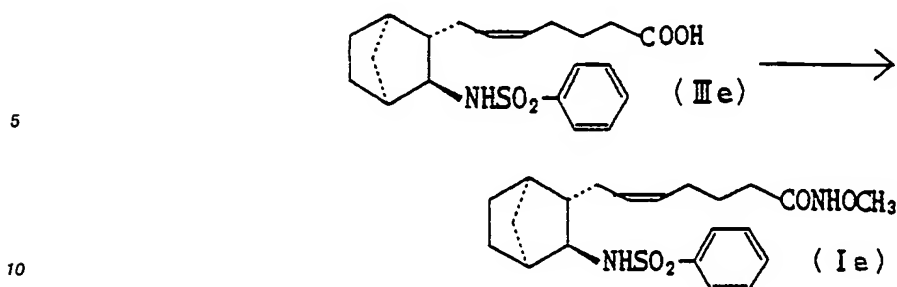
Elementary Analysis Calcd. for  $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}_5\text{S} \cdot 0.5\text{H}_2\text{O}$  (%):

C 56.55, H 6.76, N 6.94, S 7.94

Found. (%): C 56.66, H 6.65, N 7.11, S 7.74.

#### Example 5

Preparation of (1R,2S,3S,4S)-(5Z)-0-methyl-7-[3-phenylsulfonylamino-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenohydroxamic acid (Ie)



The compound (Ie) of the present invention is prepared according to the same manner as in Example 1.

15 Yield: 70.7% mp. 78-80° C  
 IR(CHCl<sub>3</sub>)  $\nu$  max: 3395, 3280, 3010, 2965, 2885, 1690, 1461, 1450, 1323, 1160, 1095, 590, 555 cm<sup>-1</sup>.  
<sup>1</sup>HNMR(CDCl<sub>3</sub>)  $\delta$  ppm: 0.92-2.26(m, 17H), 2.97-3.10(m, 1H), 3.78(s, 3H), 5.00(brs, 1H), 5.20-5.38 (m, 2H), 7.44-7.67(m, 3H), 7.87-7.92(m, 2H), 8.53-8.69(m, 1H)  
 20  $[\alpha]_D$ : +17.2±0.6° (CH<sub>3</sub>OH, 1.032%, 23.0° C)

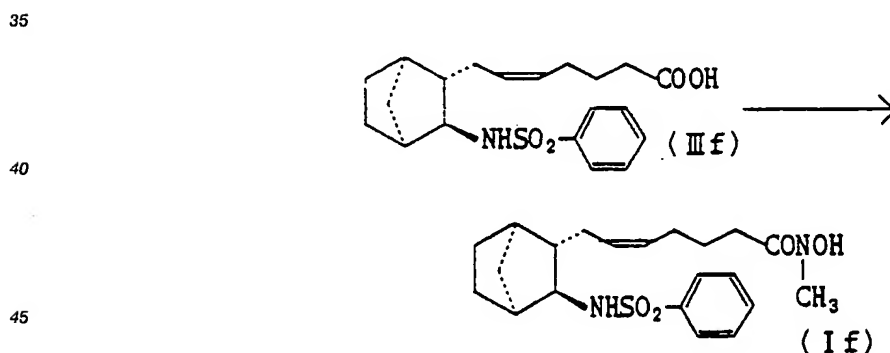
Elementary Analysis Calcd. for C<sub>21</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>S (%):

25 C 62.04, H 7.44, N 6.89, S 7.89

Found. (%): C 61.80, H 7.40, N 6.89, S 7.78.

### 30 Example 6

Preparation of (1R,2S,3S,4S)-(5Z)-N-methyl-7-(3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)-5-heptenohydroxamic acid (If)



The compound (If) of the present invention is prepared according to the same manner as in Example 1.

50 Yield: 78.7% mp. 126-127° C  
 IR(CHCl<sub>3</sub>)  $\nu$  max: 3300, 3150, 1638, 1148, 1091, 1074, 765, 723, 690cm<sup>-1</sup>.  
<sup>1</sup>HNMR(CDCl<sub>3</sub>)  $\delta$  ppm: 0.96-2.60(m, 17H), 2.90-3.09(m, 1H), 3.35(s, 3H), 5.22-5.40(m, 2H), 5.72-5.89-  
 (brs, 1H), 7.42-7.62(m, 3H), 7.84-7.95(m, 2H)  
 55  $[\alpha]_D$ : +22.9±0.6° (CH<sub>3</sub>OH, 1.011%, 25.0° C)



Elementary Analysis Calcd. for  $C_{21}H_{30}N_2O_4S \cdot 0.25H_2O$ (%):

C 61.36, H 7.48, N 6.81, S 7.80

Found. (%): C 61.40, H 7.40, N 6.72, S 7.72.

#### Effect of the invention

The compounds of the present invention have potent thromboxane  $A_2$ -receptor antagonistic activity and extremely inhibit platelet aggregation or vasoconstriction etc. caused by thromboxane  $A_2$ . This means that the compounds are useful agents as anti-thrombosis, anti-vasoconstriction. In the following Experiment are shown the inhibitory effect of the representative compounds thereof on platelet aggregation in vitro.

#### Experiment 1

##### Antagonistic Activity

(Inhibitory Effect on Platelet Aggregation in Rat)

[Material and Method]

From the abdominal artery of a male rat (Sprague-Dowley, 7 weeks old) was collected 10 ml of blood with a plastic syringe containing 1.5 ml of ACD (85 mM of sodium citrate, 70 mM of citric acid, 110 mM of glucose) and 20  $\mu$ g of prostaglandin  $E_1$ . The blood was placed in a plastic test tube, shaken moderately turning and centrifuged for 10 minutes at  $160 \times g$  to give platelet rich plasma (PRP). To the prepared PRP was added apyrase (25  $\mu$ g/ml) and the mixture was layered on 40% bovine serum albumin. The resulting mixture was centrifuged at  $1200 \times g$  for 25 minutes. The suspension of the prepared platelet pellets in a small amount of a buffer (137 mM of NaCl, 2.7 mM of KCl, 1.0 mM  $MgCl_2$ , 3.8 mM of  $NaH_2PO_4$ , 3.8 mM of Hepes, 5.6 mM of glucose, 0.035% of bovine serum albumin, pH 7.35) was applied on 10 ml of Sepharose 2B column and eluted with such a buffer to prepare washed platelets.

The platelet aggregation reaction was measured by the aggregometer (NKK HEMA TRACER 1 MODEL PAT-6A\*6M, Nikkou Bioscience).

In a measuring cuvette was placed 245  $\mu$ l of the washed platelets which concentration was adjusted to  $5 \times 10^8/\mu$ l and set in the aggregometer. The adjusted washed platelets were stirred (1000 rpm) at  $37^\circ C$  and 3.8  $\mu$ l of 0.1 M  $CaCl_2$  was added thereto. One minute later, 0.5  $\mu$ l of a solution of a test compound in dimethylsulfoxide was added and 2 minutes later, 1  $\mu$ l of collagen (Collagen reagent Horm $^\circ$ , HORMON-CHEMIE M $\ddot{u}$ nchen GMBH, final concentration 4  $\mu$ l/ml) was added as an inducer for platelet aggregation. Platelet aggregation was monitored in terms of the increase and decrease in light transmission.

Concentration of 50% inhibition for platelet aggregation was calculated from the rate of aggregation. (The rate corresponds to light transmission of a sample which was measured at 3 minutes after adding the inducer for platelet aggregation, provided that light transmissions of the washed platelets and the buffer samples are taken as 0% and 100%, respectively.)

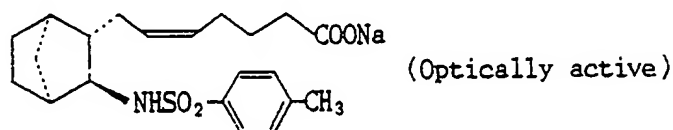
The results of the test are shown in Table 1.

Table 1

Compd. No. *	Inhibition for Platelet Aggregation IC <sub>50</sub>
Ia	12 nM
Ib	10 nM
Ic	20 nM
Ie	60 nM
If	20 nM
Rf. Compd.	2 nM

\* Compounds I a and I b were used as their sodium salts.

The reference compound is shown below.



As clearly shown by the results, the compounds of the present invention have the comparable activity for the main effect to known thromboxane A<sub>2</sub>-receptor antagonists. Since the reference compound which seems to have the most potent inhibitory activity for platelet aggregation was selected from those disclosed in JPN Kokai 63-139161, the results show the compounds of the present invention have rather lower activity than the reference compound. However it is well known that the compounds of this kind give the same pharmacological effects as those expected by oral administration, if they are intravenously administered at a 1/10 dose of the oral dose. Therefore, considered that the compounds of the present invention are suitable for intravenous administration, it is expected that a smaller dose of them than the reference compound can give the pharmacological effects comparable to those expected by oral administration of the reference compound.

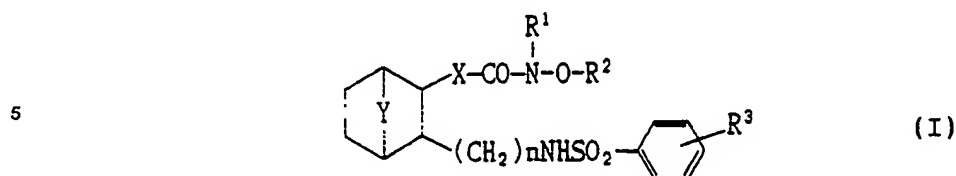
Furthermore, partial agonistic activity (activity to induce the shape change in rat platelet) was determined according to the method used for the reaction of platelet aggregation. To the washed platelets was added 0.1 M CaCl<sub>2</sub> aqueous solution and 1 minute later, the decrease in light transmission caused by the test compounds was determined to estimate the activity. As a result, the compound (Ia) gave no partial agonistic activity even up to 1000 nM, while the ED<sub>50</sub> of the reference compound was 1 nM.

The compound (Ia) of the present invention was confirmed to show substantially no partial agonistic activity and longer lasting effects as compared with known carboxylic acid derivatives, by determination of respiration inhibitory activity which is observed when the TXA<sub>2</sub>-receptor antagonist is intravenously injected to mice, and is a good index of the partial agonistic activity.

This is that the compound (Ia) of the present invention is a very suitable for intravenous injection because of having no partial agonistic activity in effect.

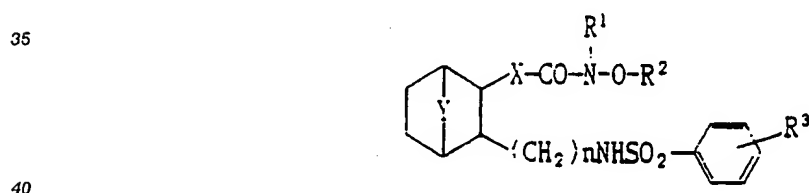
#### Claims

1. A compound represented by the formula I:



10 wherein  $R^1$  and  $R^2$  each is hydrogen or lower alkyl;  $R^3$  is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2 or a pharmaceutically acceptable salt thereof.

2. The compound claimed in Claim 1, wherein  $R^1$  and  $R^2$  each is hydrogen.
- 15 3. The compound claimed in Claim 1, which is (+)- or (-)-enantiomer.
4. The compound claimed in Claim 2, which is a (+)-enantiomer.
- 20 5. A pharmaceutical composition comprising a compound claimed in any one of Claims 1 to 4 as an effective ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.
6. The pharmaceutical composition claimed in Claim 5 for the treatment of thromboxane  $A_2$  mediated disease.
- 25 7. The pharmaceutical composition claimed in Claim 6, which is in a form of injection.
8. A compound claimed in any one of claims 1 to 4 for use in the treatment of thromboxane  $A_2$  mediated disease.
- 30 9. A method for preparing a compound represented by the formula:

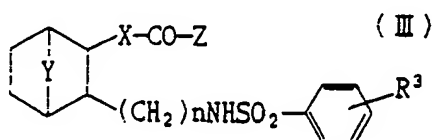


45 wherein  $R^1$  and  $R^2$  each is hydrogen or lower alkyl;  $R^3$  is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2 or a pharmaceutically acceptable salt thereof, which comprises condensing an amine of the formula (II):



wherein  $R_1$  and  $R_2$  each is the same as defined above, with a compound of the formula (III):

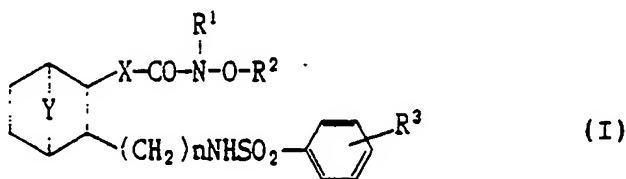
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10 wherein  $R^3$ , X, Y, and n each is the same as defined above; and Z means an electron withdrawing group.

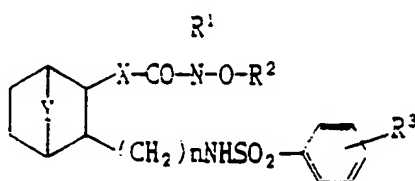
**Claims for the following Contracting State: GR**

- 15 1. A compound represented by the formula I:

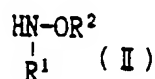


25 wherein  $R^1$  and  $R^2$  each is hydrogen or lower alkyl;  $R^3$  is hydrogen lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2 or a pharmaceutically acceptable salt thereof.

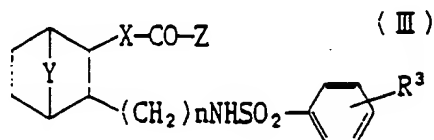
- 30 2. The compound claimed in Claim 1, wherein  $R^1$  and  $R^2$  each is hydrogen.
3. The compound claimed in Claim 1, which is (+)- or (-)-enantiomer.
4. The compound claimed in Claim 2, which is a (+)-enantiomer.
- 35 5. A compound claimed in any one of Claims 1 to 4 for use in the treatment of thromboxane  $A_2$  mediated disease.
6. A method for preparing a compound represented by the formula:
- 40



50 wherein  $R^1$  and  $R^2$  each is hydrogen or lower alkyl;  $R^3$  is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2 or a pharmaceutically acceptable salt thereof, which comprises condensing an amine of the formula (II):



wherein R<sub>1</sub> and R<sub>2</sub> each is the same as defined above, with a compound of the formula (III):

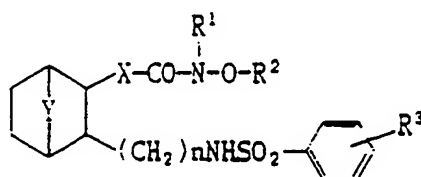


wherein R<sup>3</sup>, X, Y, and n each is the same as defined above; and Z means an electron withdrawing group.

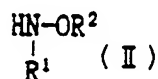
7. A method for preparing a pharmaceutical composition comprising combining a compound claimed in any one of Claims 1 to 4 as an effective ingredient, with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.

**Claims for the following Contracting State: ES**

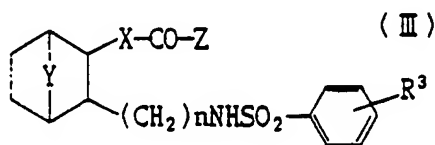
1. A method for preparing a compound represented by the formula:



wherein R<sup>1</sup> and R<sup>2</sup> each is hydrogen or lower alkyl; R<sup>3</sup> is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen; X is alkylene or alkenylene; Y is methylene or oxygen; and n is 0, 1, or 2 or a pharmaceutically acceptable salt thereof, which comprises condensing an amine of the formula (II):



wherein R<sub>1</sub> and R<sub>2</sub> each is the same as defined above, with a compound of the formula (III):



wherein R<sup>3</sup>, X, Y, and n each is the same as defined above; and Z means an electron withdrawing group.

2. The method claimed in Claim 1, for preparing a compound of the formula I wherein R<sup>1</sup> and R<sup>2</sup> each is hydrogen.
3. The method claimed in Claim 1, for preparing a compound of the formula I which is (+)- or (-)-enantiomer.

4. The method claimed in Claim 2, for preparing a compound of the formula I which is a (+)- enantiomer.
5. A method for preparing a pharmaceutical composition comprising combining a compound obtained in any one of Claims 1 to 4 as an effective ingredient, with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.

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European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 91106218.0
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 112, no. 5, January 29, 1990, Columbus, Ohio, USA SHIONOGI AND CO.;LTD "Preparation of ((benzene-sulfonamidoalkyl)bicycloheptyl)heptenoic acids as thromboxane A2 antagonists" page 549, column 1, abstract-no. 35 549u & Jpn. Kokai Tokkyo Koho JP 63-284 158 (88284158) --	1-9	C 07 D 493/08 A 61 K 31/557
A	EP - A2/A3 - 0 207 684 (E.R. SQUIBB & SONS, INC.) * Abstract *	1-9	
A	DE - A1 - 3 346 047 (E.R. SQUIBB & SONS, INC.) * Claims 1-5 *	1-9	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 493/00
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 06-06-1991	Examiner BRUS
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application I : document cited for other reasons ----- & : member of the same patent family, corresponding document			